PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 910/53	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/03353	International filing date *(day/month/year)* 10 February 2000 (10.02.2000)	Priority date *(day/month/year)* 02 March 1999 (02.03.1999)

International Patent Classification (IPC) or national classification and IPC

IPC(7): C12N 9/29, 9/24, 9/42; A61K 38/00, 38/47, 31/00 and US Cl.: lease See Supplemental Sheet.

Applicant

INSIGHT STRATEGY & MARKETING LTD.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28 September 2000 (28.09.2000)	26 June 2001 (26.06.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ponnathapu Achutharao Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/03353

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-34 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages NONE, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 35 and 36, filed with the letter of 16 May 2001 (16.05.2001)

☒ the drawings:
pages 1-8, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☒ the claims, Nos. 7-53

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/03353

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	2, 4, 5 and 6	YES
	Claims	1 and 3	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-6	NO
Industrial Applicability (IA)	Claims	1-6	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1 and 3, lack novelty under PCT Article 33(2) as being anticipated by Bartlett et al. (Immunology and Cell Biology 73: 113-124, 1995)

Bartlett et al. teach a comparative analysis of the ability of leucocytes, endothelial cells and platlets to degrade the subendothelial basement membrane. Bartlett et al. specifically teach preparation of human platlets from venous blood and resuspended in RPMI-1640 medium containing 10% FCS. Bartlett et al. further teach that both platlets and endothelial cells in suspension expressed heparanase and each of these cell suspensions were able to degrade the extracellular matrix in an extracellular matrix assay, thus these enzymes are adhered to these cells such that they are able to degrade this extracelluar matrix. Further, Bartlett et al. teach that expression of such enzymes is necessary for the adhesion, extravasation and movement of these cells through the blood vessel wall prior to entry into inflammatory sites. Applicant is reminded that as discussed in previous office actions, applicants amendment of claims to recite "for use in vivo" and "so as to enhance extravasation... of said cells in vivo", are intended "uses" of the biological preparation therefore carry no patentable weight.

Claims 1-6 lack an inventive step under PCT Article 33(3) as being obvious over Fuks et al. (US Pat No: 5,362,641), Wang et al. (J. Orthop. Res., 14 (2): 149-153 1996, abstract) and Myers et al. (Am J. Surg. 170(1): 75-83, 1995 Jul).
Fuks et al. teach a substantially purified heparanase from human SK-HEP-1 cell line and a method to purify the heparanase. They teach the use of this heparanase as the basis for a pharmaceutical composition comprising the heparanase in combination with a pharmaceutically acceptable, preferably slow releasing carrier (column 5, lines 17-30). Such a compositin is useful for the treatment of wounds and enhancement of the wound-healing process. Fuks et al. further teach that the extracellular matrix appears to be essential to the control of cell proliferation and morphogenesis and that heparan sulfate proteoglycans (HSPG), as a principal component of basement membranes plays a integral role in tissue architecture and function. A number of normal and abnormal physiological conditions and disorders are associated with the degradation of the extracellular matrix of various tissues, such as neutrophil mobilization during the inflammatory process as well as tumor cell invasion during metastasis. Thus the invading cells must be capable of producing ECM degrading enzymes in order to move through the tissue. The enzymes include in addition to heparanase, chrondroitinase, hyaluronidase and keratanase as well as other ECM degrading enzymes.
Fuks et al. teach in addition to the above function ECM degradation an additional function of heparanase is the release of growth factors from basement membranes and subendothelial ECM such as angiogenic, endothelial (ECGF) and fibroblast growth factors (FGF). FGF is essential in the proliferation of fibroblasts and virtually all other mesoderm and neuro-ectoderm-derived cells which are responsible for the production of collagen tissue. Fuks et al. teach that FGF is stored within the basement membrane and bound to heparan sulfate until an exogenous factor such as heparanase causes its release. Fuks et al. teach that heparanase may provide an effective method to mobiliz- and activate the ECM-bound FGF and hence promote the wound healing process as well as other pathological conditions which are likely to benefit from neovascularization promoted by FGF including cardiac, cerebral and peripheral ischaemic diseases associated with vascular damage. Other potential clinical applications for angiogenic factors taught by

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Fuks et al. are in processes such as ovulation, hair growth, transplantation, nerve regeneration and bone and cartilage repair.
Wang et al. teach that basic fibroblast growth factor enhances bone-graft incorporation. Specifically Wang et al. teach the implantation of bone grafts, which had been previously soaked overnight in basic fibroblast growth factor, into the proximal tibiae of recipient rats.
Myers et al. teach the transplantation of keratinocytes in the treatment of wounds.
Myers et al. teach that keratinocyte grafting can be used to treat acute traumatic and chronic non-healing wounds and the keratinocyte sheets secrete many growth factors which have effects on wound healing apart from the "take" of the keratinocyte sheet. Myers et al. show that pretreatment of the wound bed with viable dermis greatly increases the take of keratinocyte grafts.
One of ordinary skill in the art at the time of filing would have been motivated to pretreat keratinocyte grafts prior to implantation of the grafts in recipient tissue with a growth factor or other factor to stimulate integration of the graft into the recipient tissue. Such pretreatment of tissue prior to its transplantation is taught by Wang et al. Based on the teaching of Fuks et al. one of ordinary skill in the art at the time of filing would have been motivated to treat said keratinocyte grafts with heparanase as opposed to a specific growth factor in order to stimulate the release of endogenous growth factors such as FGF from the recipient tissue. As taught by Fuks et al., the use of heparanase to release FGF from its natural setting has the advantage of the cells responding locally to the endogenous natural growth factors and appropriate amount as opposed to high doses of FGF which have been shown to be toxic to various cell types including endothelial cells. Further Fuks et al. teach that heparanase has other beneficial effects on the wound healing process such as the breakdown of the ECM, a necessary part of the integration of invading or transplanted cells.
Therefore, claims 1- 6 are made obvious by Fuks et al., Wang et al. and Myers et al.

---------- NEW CITATIONS ----------

Bartlett et al. Comparative analysis of the ability of leucocytes, endothelial cells and platlets to degrade the subendothelial basement membrane: Evidense for cytokine dependence and detection of a novel sulfatase. Immunology and Cell Biology 1995, Vol. 73, pages 113-124, See entire document.

MYERS et al. Transplantation of Keratinocytes in the Treatment of Wounds. Am J. Surg. July 1995, Vol.170, pages 75-83, See entire document.